*International Journal of Neuropsychopharmacology* (2013), **16**, 1911–1925. © CINP 2013
doi:10.1017/S1461145713000540

ARTICLE

# Quetiapine and flupentixol differentially improve anterior cingulate cortex function in schizophrenia patients: an event-related potential study

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**Abstract**

Atypical antipsychotic agents are a frequently and effectively used treatment in schizophrenia and psychotic disorders. Other than conventional antipsychotics, which mainly exert their pharmacological effect in subcortical dopaminergic systems, atypical antipsychotics additionally affect partly serotonergically innervated structures within prefrontal areas, such as the anterior cingulate cortex (ACC). However, only few controlled, randomized studies have so far investigated direct and indirect effects of atypical antipsychotics on the ACC and, up until now, no clinical investigation has exclusively addressed the specific effects of quetiapine on ACC function. The present study assessed ACC function in 18 quetiapine-medicated patients and 13 flupentixol-treated patients suffering from schizophrenia by means of the error-related negativity (ERN), a neurophysiological marker of ACC function, in a pre-post design. Between-group comparisons revealed different effects of quetiapine and flupentixol on ACC function despite similar improvement in psychopathology, cognitive performance and quality of life. Whereas atypical treatment was associated with an increase in amplitudes over time, there were prolonged ERN peak latencies in patients treated with the typical agent. Moreover, treatment effects depended on baseline prefrontal cortex function in both groups. We conclude that both flupentixol and quetiapine improve prefrontal function especially in patients with weak initial ACC function which might be due to their shared affinity for serotonin receptors in frontal brain regions. However, since this affinity is more pronounced for quetiapine, patients treated with quetiapine seemed to profit more evidently concerning their prefrontal cortex function compared to patients of the flupentixol group, who exhibited a compensatory prolongation of processes.

*Received 20 December 2012; Reviewed 24 January 2013; Revised 5 April 2013; Accepted 22 April 2013; First published online 12 June 2013*

**Key words:** ACC, error-related negativity, event-related potentials, schizophrenia, treatment effects.

## Introduction

One of the neurobiological hallmarks of schizophrenic illnesses is a decreased frontal lobe function, known as cerebral 'hypo-frontality' (Ingvar and Franzén, 1974), which has been demonstrated in various studies using functional magnetic resonance imaging (fMRI), positron emission tomography (Kim et al., 2003), Zielasek et al., 2005) or near-infrared spectroscopy (Ehlis et al., 2007) particularly during cognitive challenges involving verbal fluency, Go-NoGo or working memory tasks. Another neurocognitive function that has been shown to be affected in schizophrenia concerns the action-monitoring domain (Firth and Done, 1989; Carter et al., 2001; Laurens et al., 2003) which includes the ability to internally monitor erroneous responses and has been associated with neural activity

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in the anterior cingulate cortex (ACC; Kiehl et al., 2000; Botvinick et al., 2004).

Neurobiological evidence for dysfunctional error-monitoring in schizophrenia derives primarily from event-related potential (ERP) research that targets a fronto-central negative component, termed error negativity (Ne) or error-related negativity (ERN; (Gehring et al., 1993). The ERN occurs within the first 100 ms after commission of an error and is usually followed by a positive component peaking about 200–450 ms after the incorrect response [error-positivity (Pe)]. Source localization analyses together with neuroimaging data confirm the ACC as neuroanatomical source for both components (Kiehl et al., 2000; van Veen and Carter, 2002; Herrmann et al., 2004). Behaviourally, successful action-monitoring is expressed by prolonged reaction times (RTs) in trials following erroneous responses [post-error slowing (PES)], reflecting adaptive control mechanisms that trigger more cautious behaviour in order to reduce the risk of future error commission (Botvinick et al., 2001).

Kopp and Rist (1999) were the first to demonstrate diminished ERN amplitudes in schizophrenia. Mathalon et al. (2002) confirmed this finding while also observing unusually large ERN-like waves on correct trials (correct response negativity, CRN). Similar results were reported by Alain et al. (2002) who further observed reduced PES in patients compared to controls. Finally, Morris et al. (2006) demonstrated ERN abnormalities in schizophrenia patients even under conditions that normally maximize ERN amplitudes. Regarding neurofunctional connectivity, diminished activation of the ACC and dorsolateral prefrontal cortex (PFC) in error-trials are thought to underlie action-monitoring deficits in schizophrenia (Kerns et al., 2005; Polli et al., 2008; Mathalon et al., 2009), while reduced connectivity between the ACC and cerebellar regions was additionally shown (Becerril et al., 2011). Anatomical studies confirm an involvement of the ACC in mechanisms beyond social and affective functioning, such as executive functions, motor control and behaviour monitoring (Devinsky et al., 1995; Paus, 2001) and there is some evidence for anatomical abnormalities of the ACC in schizophrenia patients that may be related to, among other symptoms, cognitive impairments (Szeszko et al., 2000; Todtenkopf et al., 2005; Fornito et al., 2009).

Given its well-known neurofunctional background and high intra- and interindividual stability (Olvet and Hajcak, 2009), the ERN might be particularly useful to investigate ACC (dys-)function in schizophrenia and monitor changes in frontal lobe function due to different antipsychotic treatment regimens [i.e. typical/conventional/first generation antipsychotics (FGAs) *vs.* atypical/second generation antipsychotics (SGAs)], which are assumed to rely on different neurobiological mechanisms of action. Although the exact cellular basis of their therapeutic action is not fully understood, previous research suggests that FGAs primarily block subcortical dopamine ($D_2$) receptors, whereas a common characteristic of SGAs is reflected in their prominent serotonin ($5\text{-}HT_{2A}$)-receptor blocking effect together with $D_2$-receptor antagonism. However, each SGA agent has its unique binding profile for other receptor types, such as histamine, muscarinic and $\alpha$-adrenergic receptors, and these drugs further differ with respect to their pharmacological characteristics *in vivo* and *in vitro* (Suzuki et al., 2013).

Although superior effects of atypical over typical agents regarding clinical potency are intensively discussed, different studies confirm positive effects of SGAs on the frontal lobes and related neurocognitive function (e.g. Meltzer and McGurk, 1999; Ehlis et al., 2005; Woodward et al., 2005; Riedel et al., 2007b) by an enhancement of dopamine, 5-HT and acetylcholine levels in prefrontal regions (Ichikawa et al., 2002; Peuskens et al., 2005; Meltzer and Massey, 2011). However, recent meta-analyses indicate that cognitive advantages of SGAs contrasted with FGAs reach only low effect sizes that are sometimes even negligible (Thornton et al., 2006; Goldberg et al., 2007; Hill et al., 2009). Overall, there is a consensus that existing antipsychotics, while successfully improving positive psychotic symptoms, affect cognitive deficits only in part and not satisfyingly (Stoeber et al., 2009). Moreover, to date there is no clear evidence for a general superiority of SGAs over FGAs regarding clinical symptom improvement and long-term symptom reduction (Rosenheck et al., 2003; Hasan et al., 2013), as methodologically good meta-analyses are rare and results highly dependent on the respectively compared agents, dosages or the occurrence of side-effects (Davis et al., 2003; Leucht et al., 2003, 2009). Therefore, future research on pharmacological treatment efficacy in schizophrenia can certainly benefit from neurophysiological studies integrating clinical, cognitive and neurobiological aspects of symptom change.

In a recent study, electrophysiological findings suggested a differential baseline PFC function× treatment response interaction to FGAs and SGAs. In a prospective study including different FGAs and SGAs, patients exhibiting pronounced hypofrontality showed stronger symptom improvement under atypical treatment, whereas patients with relatively

strong baseline PFC function improved more markedly under conventional medication (Ehlis et al., 2012).

The present study aimed at extending these findings by investigating the effects of two specific antipsychotics on symptomatology and ACC function in a group of schizophrenia patients. Specifically, the effects of one SGA (quetiapine; Seroquel®) were compared to a conventional agent (flupentixol; Fluanxol®) regarding ERP markers of PFC function, neurocognitive performance and psychopathology. Flupentixol is a thioxanthene derivative showing strong, balanced $D_1$- and $D_2$-receptor antagonism, together with a moderate $\alpha$1-antagonism and an antiserotonergic and weak antihistaminergic effect (Patteet et al., 2012). Due to its elevated antiserotonergic effect, compared to many other FGAs, flupentixol is sometimes referred to as the 'atypical' FGA.

So far, previous fMRI studies seem to indicate beneficial effects of quetiapine on prefrontal activation during cognitive tasks (Jones et al., 2004; Stip et al., 2005). A clinical trial on the effects of quetiapine compared with olanzapine further reported a slight superiority of quetiapine concerning attention and cognitive performance (Riedel et al., 2007a). This finding could not be explained by side-effects, as no extra-pyramidal symptoms (EPS) occurred in any of the groups. However, sample size in that study suffered from high drop-out rates, leading to a restricted external validity of this outcome. Generally speaking, only few controlled studies have been conducted and, to our knowledge, no prospective studies have directly examined the impact of quetiapine on the ACC.

We hypothesized to find a positive effect of quetiapine on ACC function as indicated by a normalization of ERN/Pe amplitudes. Considering that flupentixol shows, at least to some extent, antiserotonergic receptor binding, we also expected some improvement regarding ACC function within the flupentixol-treated group. However, we suggest generally more pronounced improvements following SGA compared to FGA treatment, both on the neurophysiological and on the behavioural level (cognitive performance and PES).

## Method

### *Study design and participants*

A total of 59 schizophrenia patients (aged 19–60 yr) were enrolled in this prospective study, which was designed as a randomized, rater-blind treatment survey.

Exclusion criteria were current co-morbidities with Axis I disorders, severe somatic or neurological conditions, pregnancy, intolerance or lack of response to quetiapine or flupentixol in previous treatments. Patients were also excluded if they were posing an imminent risk of suicide or danger to self or others. After complete study description, written informed consent was obtained. The study was approved by the Ethics Committees of the Universities of Wuerzburg and Tuebingen and all procedures were in accordance with the latest version of the Declaration of Helsinki.

Patients were recruited at the Psychiatric University Hospital of Wuerzburg ($n$=41) and Tuebingen ($n$=18; both Germany), respectively. Three data sets were excluded because of noisy EEG data or an insufficient number of error trials; 19 patients were excluded for the following reasons: switch of drug category from baseline to follow-up ($n$=4); co-morbid obsessive-compulsive disorder ($n$=2); discontinuation of study participation for personal reasons ($n$=13).

The remaining patients were treated with quetiapine ($n$=22) or flupentixol ($n$=13) and investigated throughout 30 d. Pre-medication with either one in the final three months prior to study enrolment was another exclusion criterion. However, some patients additionally received at least one co-medication with low to medium doses of benzodiazepines ($n$=17), tri- or tetracyclic antidepressants ($n$=11), anti-epileptics ($n$=3), lithium ($n$=3) or biperiden ($n$=2). The latter, anticholinergic medication was however not administered throughout the entire study period: one patient received biperiden at the beginning of the study and the second started biperiden intake just a few days prior to study completion. Neurophysiological investigations took place within 1 wk after start of treatment (baseline) and again after approximately 30 d (follow-up).

Patients were diagnosed with paranoid ($n$=15), disorganized ($n$=6) or catatonic schizophrenia ($n$=3), schizoaffective ($n$=9) or brief psychotic disorder ($n$=2). Based on the Structured Clinical Interview for DSM-IV (Wittchen et al., 1997) four patients were additionally diagnosed with nicotine dependence (305.10), cannabis abuse (305.20) or dependence (304.30); one patient suffered from social phobia (300.23) and one from borderline personality disorder (301.83). Several psychopathological scales [Positive and Negative Symptom Scale (PANSS); Global Assessment of Functioning (GAF); Brief Psychiatric Rating Scale (BPRS); Hamilton Depression Rating Scale (HAMD)] and a German self-assessment scale for the subjective quality of life [Berliner Lebensqualitätsprofil (BLQP)] were additionally applied four times throughout the study (day 1/baseline;

**Table 1.** Overview of the baseline characteristics of the quetiapine and the flupentixol group, respectively

| Independent variable(s) | Quetiapine group | Flupentixol group |
|---|---|---|
| Individual variables | | |
| Age (yr) | 34.67 (12.69) | 39.08 (14.47) |
| Gender (absolute frequencies) | 11 male, 7 female | 6 male, 7 female |
| Education (yr) | 9.89 (1.37) | 10.23 (1.30) |
| Hospitalization (mean frequencies) | 1.68 (2.25) | 3.92 (4.39) |
| Duration of disease (months) | 85.00 (84.18) | 78.69 (105.16) |
| Pharmacological treatment (mean values) | | |
| CPZ-equivalent dose | 372.20 (296.67) | 526.92 (324.43) |
| Co-medication (absolute frequencies) | | |
| SSRIs | 5 | 6 |
| Lithium | 1 | 2 |
| Biperiden | 0 | 2 |
| Anticonvulsants | 2 | 1 |
| Benzodiazepine | 8 | 9 |
| Clinical outcome (mean values) | | |
| PANSS positive | 14.94 (5.41) | 16.54 (6.01) |
| PANSS negative | 17.18 (5.42) | 20.38 (7.69) |
| PANSS global | 33.94 (4.83) | 42.36 (11.41) |
| BPRS | 41.63 (7.16) | 50.38 (10.19) |
| GAF | 50.68 (14.18) | 46.09 (16.15) |
| Side-effects | | |
| EPS | 0.44 (0.70) | 2.45 (4.22) |

CPZ, Chlorpromazine; SSRIs, selective serotonin re-uptake inhibitors; PANSS, Positive and Negative Symptom Scale; BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Functioning; EPS, extra-pyrimidal symptoms. Values are mean (S.D.).

day 10; day 20; day 30/follow-up). For the PANSS, four different measures including the three subscales ('positive symptoms', 'negative symptoms' and 'general psychopathology') and the total score were assessed. Concerning the BLQP, 'contentment with life in general' and 'contentment with psychological health' were regarded along with a quotient indicating general quality of life (QoL). Neuropsychological tests [Stroop Task; Trail Making Test (TMT) parts A & B; Verbal Fluency Test (VFT) letter & category version] were conducted at baseline and follow-up.

First data inspection and analyses revealed significant group differences regarding mean baseline ERN amplitudes, averaged over the target electrodes (FCz, Cz; $t_{33}=-2.70$, $p<0.05$). In order to ensure clearly interpretable outcomes, medication groups were matched for baseline differences, leading to a final sample size of $n=18$ (quetiapine) *vs.* $n=13$ (flupentixol). Group matching was realized through an adjustment of the numerically larger quetiapine group (QG), as a reduction of the QG size helped to reduce general variance differences between the initial groups ($n=22$ *vs.* $n=13$). Therefore, subjects from the QG were sorted by mean ERN peak values at baseline. Subjects with highest derivation from the ERN group mean were subsequentially excluded until the significant baseline difference between the QG and the flupentixol group (FG) had vanished (cut-off: $\alpha>0.10$).

Resulting groups (see Table 1 for baseline group characteristics) did not differ in age ($t_{29}=-0.90$, $p=0.38$), gender ($\chi^2=0.68$, $p=0.41$), years of education ($t_{29}=-0.07$, $p=0.49$) and mean duration of disease ($t_{28}=0.18$, $p=0.86$). There was a slight but not significant trend regarding differences in hospitalization ($t_{17}=-1.70$, $p=0.11$). Mean daily chlorpromazine-equivalent doses (after Woods, 2003; Bazire, 2005) at baseline (quetiapine: 372.20±296.67; flupentixol: 526.92±324.43) and follow-up (414.81±239.34 *vs.* 537.69±409.54) did not differ between groups (baseline: $t_{29}=-1.37$, $p>0.10$; follow-up: $t_{29}=-1.05$, $p>0.20$); neither did the baseline occurrence of EPS ($t_{29}=-1.56$, $p=0.15$). Co-medication with selective serotonin reuptake inhibitors (SSRIs; $\chi^2=0.89$; $p=0.37$), lithium ($\chi^2=0.74$; $p=0.39$), biperiden ($\chi^2=1.35$; $p=0.25$), anticonvulsants ($\chi^2=0.14$; $p=0.71$) or benzodiazepine ($\chi^2=1.48$; $p=0.23$) was also equal between groups. On the neurophysiological level, matched ERN/CRN values (ERN: $t_{29}=-1.46$, $p>0.10$; CRN: $t_{29}=1.68$, $p>0.10$) and also Pe amplitudes did not differ at baseline ($t_{29}=-0.78$, $p=0.94$). Concerning baseline psychopathology, groups only differed with respect to the general psychopathology subscale of the PANSS ($t_{16}=-2.55$, $p<0.05$) and also in the related BPRS scores ($t_{21}=-2.62$, $p<0.05$), whereas negative and positive symptoms did not differ ($-1.28<t<-0.76$, $0.22<p<0.45$). The same was true for HAMD ($t_{27}=0.02$, $p=0.98$) and GAF scores ($t_{25}=0.78$, $p=0.44$).

### *Experimental paradigm*

Participants performed a modified Eriksen flanker task as described in previous publications (Ehlis et al., 2011). Briefly, different combinations of arrows were presented, with a centrally displayed stimulus serving as target pointing right or left and four flankers oriented in the same (congruent condition) or opposite direction (incongruent condition). Subjects were instructed to indicate the direction of the target arrow via button press. Directly after, visual feedback

was given regarding the correctness of the response (correct/incorrect/slow). To enhance error probability, subjects were instructed to adjust their RT every time they received a 'too slow' feedback. The corresponding RT threshold was individually calculated based on the median of RTs in the training block. After the practice block, participants performed a total of 400 trials with a break after 200 trials.

### *EEG recording*

Measurements took place in a sound-attenuated, electrically shielded room at the Psychiatric University Hospitals Tuebingen and Wuerzburg. EEG was recorded from 32 scalp electrodes embedded in an elastic cap placed according to the International 10/20-System (Jasper, 1958). To identify eye movement artefacts, activity was recorded from three additional electrodes, one placed below the right eye and two placed at the lateral canthi of both eyes. The ground electrode was placed on the forehead and FCz was used as recording reference. Impedances were kept below 5 k$\Omega$. Data were recorded with a 64-channel DC-amplifier and the software Vision Recorder (Brain Products, Germany). All physiological data were digitalized at 1000 Hz and filtered online at 0.1–100 Hz.

### *Data analysis*

Behavioural data (response type, RTs) were recorded via Presentation (Neurobehavioral Systems Inc., USA). PES was determined by subtracting RTs in trials following correct responses from RTs in trials following errors. ERPs were analysed using Vision Analyser 2.0 (Brain Products, Germany). After visual inspection of EEG recordings, all data were high-pass (0.1 Hz) and low-pass (70 Hz; 48db/oct) filtered before eye movement artefact correction was performed (Gratton et al., 1983) and data were transformed to an average reference. Response-locked epochs (−150–750 ms relative to button press) were created for each trial. Segments containing amplitudes exceeding ±70 $\mu$V or voltage-steps of >70 $\mu$V/ms were excluded. Correct but slow responses were discarded. In accordance with previous studies (Olvet and Hajcak, 2009; Pontifex et al., 2010), data sets with fewer than six artefact-free segments per condition were excluded. ERN and Pe peaks were individually determined in the averaged data of both conditions within pre-defined time-windows (ERN/Ne: 0–100 ms, FCz and Cz; Pe: 100–210 ms, Cz). Relative (peak-to-trough) amplitudes were used to quantify the ERN with respect to the preceding positive peak. Pe amplitudes were determined as absolute peak values. The analysis was performed with a baseline correction (–200 to –100 ms before the button press).

### *Statistics*

Generally, data were analysed through 2×2 analyses of variance (ANOVAs) for repeated measures comprising the inner-subject factor 'time' (baseline *vs.* follow-up) and the between-subject factor 'medication' (quetiapine *vs.* flupentixol). Analyses of flanker task data (behavioural+ERPs) additionally comprised the inner-subject factor 'response type' (correct *vs.* incorrect); ANOVAs of the ERN moreover included the factor 'electrode' (FCz, Cz). Because psychometric assessments and QoL measures were obtained four times, the within-subject factor 'time' comprised four levels for all corresponding variables (for the QoL measures, reduced 2×2 ANOVAs were conducted due to many missing values at the two assessment points in-between baseline and follow-up). Finally, based on Ehlis et al. (2012), ANOVAs of ERN peak values (as main target variable) comprised the between-subject factor 'hypofrontality' (low *vs.* high difference between ERN and CRN baseline amplitudes) to investigate effects of baseline PFC function on treatment outcomes. To prevent $\alpha$-error accumulation due to multiple testing, a Bonferroni–Holm correction was applied to adjust the significance level of $\alpha = 0.05$, leading to corrected $\alpha$-levels of $0.0071 < p < 0.05$ for psychometric analyses, $0.01 < p < 0.05$ for neurocognitive data and $0.0167 < p < 0.05$ for the QoL measures. To correct degrees of freedom in the ANOVAs, the Greenhouse–Geisser procedure was used when indicated. One-factorial ANOVAs and two-tailed $t$ tests for matched or independent samples were used for *post hoc* analyses. Equality of variances was tested through Levene's $F$ test and corrections were performed when necessary.

In order to analyse the relationship between error-related neural responses indicated by ERP data, psychopathology and neuropsychological performance, Pearson's correlation coefficients were calculated between CRN/ERN peaks (Cz) and psychopathology measures in addition to neuropsychological scores separately for baseline and follow-up. Whenever group differences were observed in any of these variables, separate correlation analyses were performed for both experimental groups. Two-sided testing procedures and Bonferroni–Holm corrections were used, leading to a corrected $\alpha = 0.007$–$0.05$ for ERP/psychopathology and 0.0083–0.05 for ERP/neuropsychology correlation coefficients.

**Table 2.** Behavioural data from the flanker task separately for the quetiapine and flupentixol groups

| | Quetiapine group ($n$=18) | | | | | Flupentixol group ($n$=13) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | Follow-up | | $t$ values | Baseline | | Follow-up | | $t$ values |
| | Mean | S.D. | Mean | S.D. | (d.f.=17) | Mean | S.D. | Mean | S.D. | (d.f.=12) |
| $n$ (correct) | 292.56 | 101.70 | 319.39 | 103.16 | −2.83* | 233.84 | 110.99 | 303.62 | 100.94 | −2.72* |
| $n$ (error) | 69.11 | 51.67 | 52.78 | 48.16 | 2.01 | 60.53 | 47.35 | 52.85 | 40.61 | 0.93 |
| RT (correct) | 470.88 | 113.55 | 435.82 | 93.26 | 3.56** | 633.03 | 164.85 | 584.91 | 128.31 | 2.71* |
| RT (error) | 412.93 | 147.06 | 392.39 | 112.47 | 0.92 | 596.49 | 178.30 | 552.40 | 196.81 | 1.35 |
| RT (post-correct) | 455.97 | 110.54 | 423.81 | 89.86 | 3.40** | 626.08 | 164.97 | 568.98 | 134.25 | 3.17** |
| RT (post-error) | 484.24 | 124.96 | 445.36 | 102.11 | 2.26** | 627.20 | 179.11 | 610.71 | 159.72 | 0.62 |
| Accuracy | 0.66 | 0.23 | 0.72 | 0.23 | −2.83** | 0.53 | 0.25 | 0.69 | 0.23 | −2.72* |

Mean, Arithmetic mean; d.f., degrees of freedom in the respective $t$ statistics; RT, reaction time.
* Significant $t$ values with regard to an uncorrected significance level ($p$<0.05).
** Significant $t$ values with regard to a Bonferroni-corrected significance level applied for each group (quetiapine group *vs.* flupentixol group) and response type (correct *vs.* error; $p$<0.0125).

## Results

### *Behavioural data*

For mean RTs, the 2×2×2 ANOVA revealed significant main effects of response type ($F_{1,29}$=17.19, $p$<0.0001, $\eta^2$=0.37), time ($F_{1,29}$=7.57, $p$<0.01, $\eta^2$=0.21) and medication ($F_{1,30}$=11.57, $p$<0.01, $\eta^2$=0.29), with no significant interactions (all $F$<1, n.s.). Responses were faster in erroneous than correct trials, at follow-up compared to baseline and in the QG compared to the FG (see Table 2). Response accuracy (percentage of correct responses) changed significantly over time ($F_{1,29}$=15.71, $p$<0.0001, $\eta^2$=0.35), with enhanced accuracy from baseline to follow-up, but did not differ between groups at any time ($F$<1, n.s.). 2×2 ANOVA for PES revealed a significant time×medication interaction ($F_{1,30}$=5.04, $p$<0.05, $\eta^2$=0.15), with significantly greater improvement in PES over time in the FG (baseline: 1.11±55.30 ms; follow-up: 45.85±63.47 ms) compared to the QG (28.27±44.99 *vs.* 21.22±39.34 ms; $t_{29}$=−2.24, $p$<0.05). In the QG, accuracy tended to correlate negatively with EPS at both time points ($r_{EPS1,ACC1}$=−0.49, $p$<0.05; $r_{EPS2,ACC2}$=−0.48, $p$<0.05), whereas in the FG, there were no such relationships.

### *ERP data – amplitudes*

For the ERN, the 2×2×2×2×2 ANOVA revealed a main effect of response type and a significant three-way electrode×time×medication interaction (see Table 3). Subsequent ANOVAs calculated separately for the two electrode positions showed that the time×medication interaction was only observed at Cz ($F_{1,27}$=5.41, $p$<0.05, $\eta^2$=0.17; see Fig. 1*b*). Therefore, additional ANOVAs were performed only at this electrode position.

The respective 2×2×2×2 (response type×time×medication×hypofrontality, see Table 3) ANOVA revealed significant main effects of response type and time. Furthermore, significant 2×2 interactions occurred as follows: response type×medication; time×medication (see earlier); response type×hypofrontality. The latter interaction was additionally affected by the factor time. Subsequent 2×2 (response type×time) ANOVAs were conducted separately for each median group of hypofrontality. For patients with strong baseline PFC function, only a significant main effect of response type was found ($F_{1,14}$=30.59, $p$<0.0001, $\eta^2$=0.69), indicating higher ERP amplitudes on erroneous compared to correct responses. In contrast, patients with weak baseline PFC function showed a significant time effect ($F_{1,15}$=9.60, $p$<0.01, $\eta^2$=0.39) and a significant response type×time interaction ($F_{1,15}$=6.97, $p$<0.05, $\eta^2$=0.32), with significant enhancements of ERP amplitudes from baseline to follow-up for errors ($t_{15}$=3.25, $p$<0.01), but not for correct trials ($t_{15}$=−0.16, n.s.; see Fig. 2).

*Post hoc* analyses of the response type×medication and time×medication interactions revealed significant amplitude differences between correct and erroneous trials in the QG ($t_{17}$=5.67, $p$<0.0001), with higher amplitudes after errors than correct responses, whereas amplitudes in the FG were similar for both response types ($t_{12}$=1.40, $p$=0.19; see Fig. 3). Moreover, *post hoc* results indicated a significant increase of mean ERN/CRN values in the QG ($t_{17}$=4.12, $p$<0.001)

**Table 3.** Overview of all significant main and interaction effects of respective independent variables of the 2×2×2×2×2 (response type×time×medication×hypofrontality×electrode) and the 2×2×2×2 (response type×time×medication×hypofrontality; only at Cz) analysis of variance (ANOVA) for repeated measures on ERN/CRN peak values

| Independent variable(s) | Levels | *F* values | *p* values | $\eta^2$ |
|---|---|---|---|---|
| 2×2×2×2×2 ANOVA | | | | |
| Response type | Correct *vs.* erroneous response | 18.165 | 0.0002 | 0.40 |
| Response type×electrode×medication IA | Correct *vs.* erroneous response; Fz *vs.* Cz; quetiapine *vs.* flupentixol | 4.47 | 0.04 | 0.14 |
| 2×2×2×2 ANOVA | | | | |
| Response type | Correct *vs.* erroneous response | 23.20 | 0.00005 | 0.46 |
| Time | Baseline *vs.* follow-up | 4.45 | 0.04 | 0.14 |
| Response type×medication IA | Correct *vs.* erroneous response; quetiapine *vs.* flupentixol | 4.36 | 0.045 | 0.14 |
| Time×medication IA | Baseline *vs.* follow-up; quetiapine *vs.* flupentixol | 5.41 | 0.03 | 0.17 |
| Response type×hypofrontality IA | Correct *vs.* erroneous response; high *vs.* low initial ACC function | 4.35 | 0.047 | 0.14 |
| Response type×hypofrontality×time IA | Correct *vs.* erroneous response; high *vs.* low initial ACC function; baseline *vs.* follow-up | 5.41 | 0.03 | 0.17 |

ERN, Error-related negativity; CRN, correct response negativity; IA, Interaction; $\eta^2$, measure of effect size (partial $\eta^2$); ACC, anterior cingulate cortex.

from baseline (−2.80±1.34 μV) to follow-up (−4.05±1.95 μV), but no change in ERN/CRN amplitudes over time in the FG (−2.81±1.61 μV *vs.* 3.15±1.97 μV; $t_{12}=0.65$, $p=0.53$).

For the Pe, the 2×2×2 ANOVA revealed a main effect of response type ($F_{1,29}=16.60$, $p<0.001$, $\eta^2=0.36$), indicating higher amplitudes in erroneous (5.70±3.96 μV) compared to correct trials (2.83±2.99 μV). Moreover, a significant time×medication interaction ($F_{1,29}=7.20$, $p<0.05$, $\eta^2=0.20$) revealed generally higher Pe values at follow-up compared to baseline in the QG ($t_{18}=-2.21$, $p<0.05$), whereas Pe amplitudes did not significantly change over the course of flupentixol treatment, with numerically even slightly decreased Pe values over time ($t_{12}=1.63$, $p=0.12$; see Fig. 1*a*).

### *ERN and Pe latencies*

With regard to the ERN, a significant time×medication effect was found ($F_{1,29}=4.05$, $p=0.05$) with an increase in peak latency within the FG (24.27±18.81 *vs.* 42.04±18.65 ms; $t_{18}=-1.97$, $p=0.05$) that was not observed in the QG (27.56±20.88 *vs.* 25.42±18.65 ms; $t_{18}<1$, n.s.). In contrast, there were no effects of any factor on Pe peak latencies ($F_{1,29}<1$, n.s).

### *Psychopathology and QoL*

ANOVAs (4×2) revealed significant time effects for the PANSS subscales 'positive symptoms' and 'general psychopathology', the PANSS total score, BPRS, HAMD and GAF score ($8.74<F<29.52$, $p<0.001$, $0.33<\eta^2<0.58$). Concerning the PANSS subscale 'negative symptoms', the time effect was marginally significant ($F_{3,63}=3.20$, $p=0.03$). The effect of time was not qualified by medication for any of the psychopathology measures. We further observed a main effect of medication for BPRS scores ($F_{20,1}=8.65$, $p<0.01$, $\eta^2=0.30$), indicating overall more severe symptomatology in the FG than the QG (see Fig. 4).

Due to a relatively large number of missing QoL values between baseline and follow-up (see earlier) only 2×2 ANOVAs were conducted for the QoL measures. There was a significant effect of time regarding the contentment with psychological health ($F_{1,27}=8.64$, $p<0.01$, $\eta^2=0.24$) and a marginally significant time effect on contentment with life in general ($F_{1,25}=4.76$, $p=0.03$, $\eta^2=0.16$), signalling an increase in life quality across medication groups. No other main effects or interactions were observed.

### *Neuropsychology*

For the VFT and TMT measures 2×2 ANOVAs did not result in significant main or interaction effects ($0.01<F<3.33$, n.s.). However, there was a significant effect of time concerning the Stroop test ($F_{1,28}=6.38$, $p<0.05$, $\eta^2=0.19$), indicating faster performance at follow-up (107.38±28.99 s) compared to baseline (120.81±31.38 s) across experimental groups.

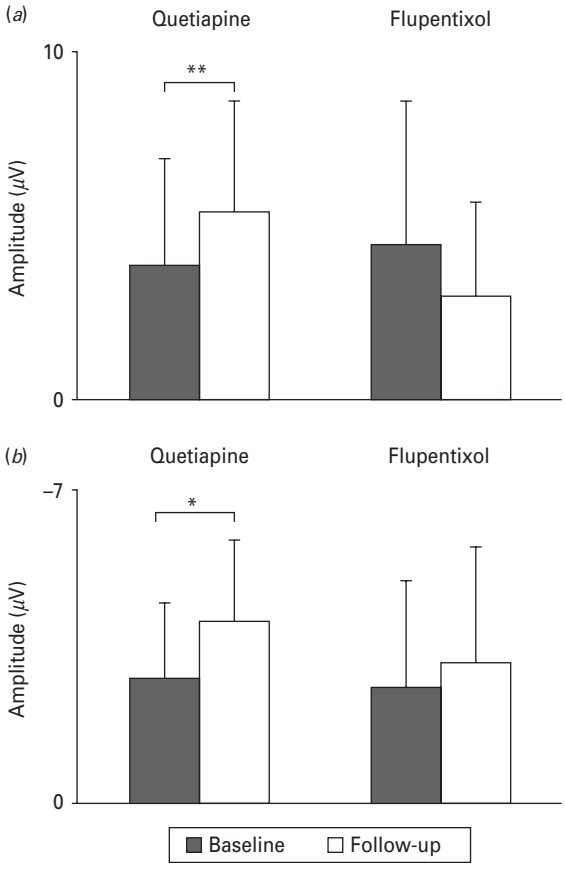


**Fig. 1.** Illustration of the two-way time × medication interaction for error positivity (Pe; *a*) and error-related negativity (ERN) peak values (*b*), respectively. Dark grey bars represent baseline ERN and Pe values; white bars reflect ERN/Pe amplitudes at follow-up. Error bars represent S.D. * $p<0.05$, ** $p<0.001$.

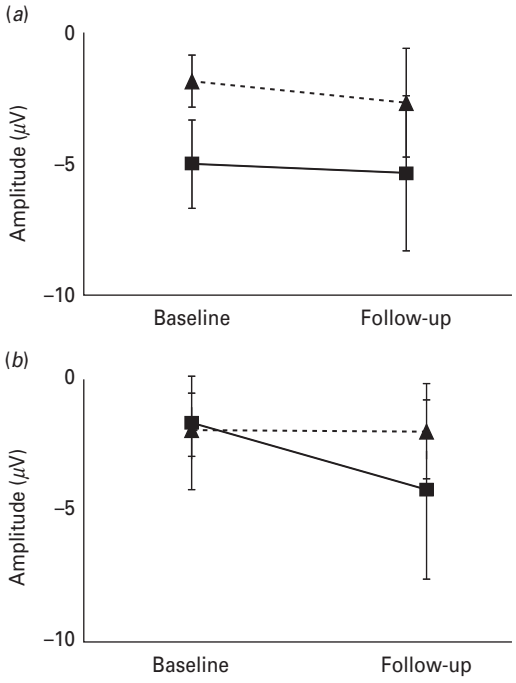


**Fig. 2.** Graphic illustration of the three-way condition × time × hypofrontality interaction for mean correct response negativity (CRN)/error-related negativity (ERN) amplitudes. Triangles (dashed line) indicate mean peak values after correct responses (average CRN amplitudes); squares (solid line) indicate peak values after error trials (average ERN amplitudes). (*a*) Median group with strong baseline prefrontal cortex (PFC) function; (*b*) Median group with weak initial PFC function. Error bars represent S.D.

### *Relationship between neural activity and psychopathology/neuropsychology*

At baseline, neither CRN nor ERN or Pe values correlated significantly with any of the psychopathology or neuropsychology measures. Regarding follow-up, analyses revealed significant positive correlations as follows: $r_{ERN,BPRS}=0.51$, $p<0.0071$; $r_{ERN,PANSS\_negative}=0.50$, $p<0.0083$; $r_{ERN,PANSS\_positive}=0.43$, $p<0.017$. Moreover, GAF scores correlated negatively with ERN values ($r_{ERN,GAF}=-0.50$, $p<0.016$). Neither CRN/ERN peak values nor peak latencies correlated with chlopromazine-equivalent doses, medication blood level, or EPS at one of the two measurement time-points.

## Discussion

The present study was conducted to (1) directly investigate the effect of antipsychotic treatment on ACC function and (2) compare the effect of one SGA (quetiapine) with one FGA (flupentixol) on cognitive performance, psychopathology and ACC function in patients suffering from schizophrenia.

Besides psychotic and affective symptoms, cognitive impairments represent a core deficit in schizophrenia that is related to a broad spectrum of functional disability. Cognitive abilities range between one and two standard deviations below the norm in schizophrenia patients (Heinrichs and Zakzanis, 1998) and constitute a rather persistent feature of the disease (Nopoulos et al., 1994; Hoff et al., 1999). Pointing to their significance, previous research indicates that cognitive deficits in schizophrenia are linked to a number of other domains (Green, 1996; McGurk and Meltzer, 2000; Keefe and Harvey, 2012), such as emotion regulation, delusions and social functioning, and their role as a predictor of functional outcome during clinical stabilization has been discussed (Green et al., 2004; Nuechterlein et al., 2011). Based on recent approaches suggesting psychopharmacological

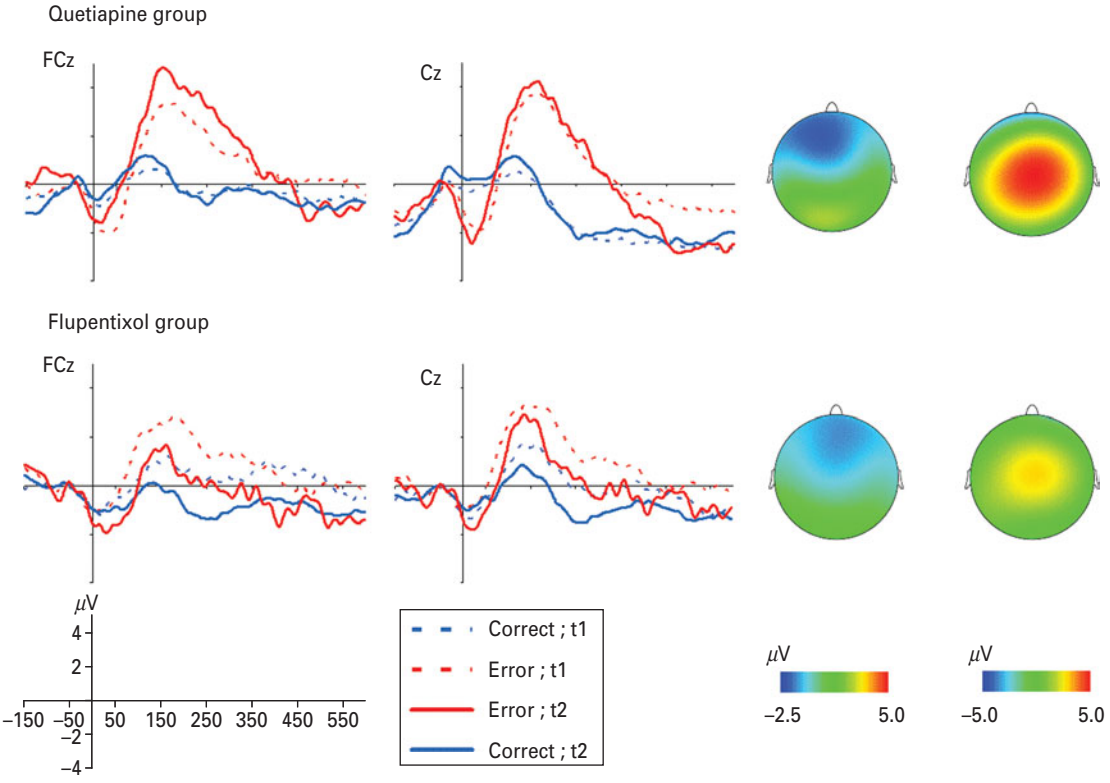


**Fig. 3.** Event-related potential waves for the quetiapine group and the flupentixol group after correct *vs*. error trials respectively: t1, baseline; t2, follow-up at the two electrode positions FCz and Cz. Respective topographic maps (depicting peaks at baseline measurement) of the error-related negativity and error positivity for each group are illustrated on the right.

interventions to treat prominent cognitive deficits (Green et al., 2004; Hill et al., 2009; Chou et al., 2012), it is of high relevance to elucidate the efficacy of different antipsychotic groups (e.g. FGAs *vs*. SGAs) in general, and of certain agents in particular (as these comparisons may have stronger practical implications), for the treatment of neurocognitive deficits in schizophrenia.

A potentially superior effect of atypical antipsychotics on ACC activation and neurocognitive functioning is currently under debate (see Ehlis et al., 2012). Aiming at this critical issue, we compared a quetiapine-medicated patient group with a matched group treated with flupentixol for 30 d. Neurophysiologically, we found a general enhancement of ERN/CRN amplitudes in quetiapine-treated patients only. Analogue effects were observed for the Pe, which increased significantly in the QG, but not in the FG. As both groups did not differ, after matching for electrophysiological responses, with regard to age, gender, education, history of the disease and co-medication as well as baseline ERPs, the effects cannot be attributed to respective baseline group disparities. The only group difference was found between global psychopathology (PANSS) and BPRS scores at baseline, pointing to slightly worse general psychopathology in the FG. However, we found that these measures were not related to electrophysiological responses (ERN/CRN and Pe) in any of the groups, which argues against an influence on the observed effect of antipsychotic medication.

These findings suggest a positive effect of quetiapine treatment on ACC action-monitoring processes; concurring with studies reporting beneficial effects of SGAs on PFC functions (see Abi-Dargham and Laruelle, 2005). Although the reported effect was not specific for erroneous responses, the consistency of the quetiapine-related ERP enhancement indicates a reliable medication effect on prefrontal activity. Moreover, it has been argued that the CRN may also be related to basal action-monitoring processes (Vidal et al., 2003).

In contrast to the quetiapine findings, we observed an increase in ERN latencies under flupentixol. We therefore suggest that treatment with both agents affects action-monitoring processes; however, whereas quetiapine fosters an intensification of action-monitoring (reflected by increased ERP amplitudes),

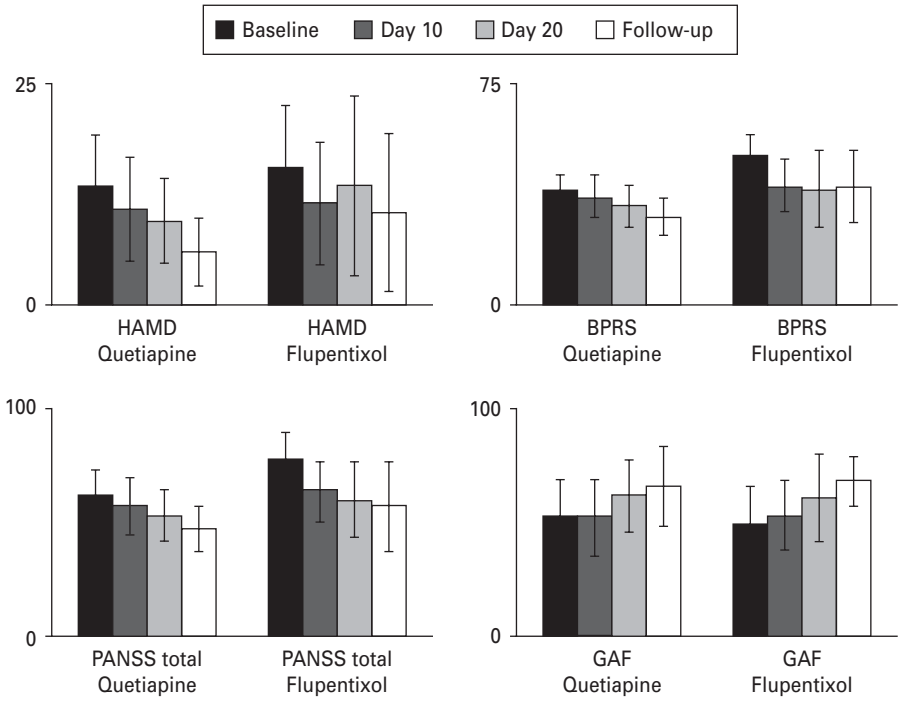


**Fig. 4.** Illustration of time-course in psychiatric symptoms and social functioning within the quetiapine and flupentixol experimental groups. Error bars represent the respective S.D. HAMD, Hamilton Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Symptom Scale; GAF, Global Assessment of Functioning.

flupentixol-treated patients show a temporal extension of processes indicated by increased ERN latencies, potentially compensating for action-monitoring impairments by prolonged cognitive processes. In line with this interpretation, flupentixol-medicated patients showed improved PES over time, reflecting the behavioural consequence of the extended action-monitoring process. The effectiveness of this compensational mechanism is also reflected by cognitive improvements within the FG that showed, similarly to quetiapine-medicated patients, improved Stroop performance. We ascribe this cognitive improvement to enhanced action-monitoring processes. Partly in line with this interpretation, Morrens et al. (2008) reported reduced processing speed during a symbol–digit–substitution test in schizophrenia patients treated with FGAs (*vs.* SGAs), with no group differences in neuropsychological performance. In light of our findings, this 'slowing' may reflect a compensational lengthening of action-monitoring processes in conventionally medicated patients to achieve adequate task performance.

The present results differ from previous findings of our group showing a decline in neurocognitive performance in patients treated with FGAs (Ehlis et al., 2012). However, in this previous study, a heterogeneously medicated group was considered, with only 25% of patients receiving solely flupentixol. As some of the administered FGAs, especially haloperidol, are known to more negatively affect executive functions than others (Keefe et al., 2003; Lindenmayer et al., 2007), we suggest that the contrary outcome in Ehlis et al. (2012) was caused by the contribution of other high-potency agents. The action-monitoring improvement in our FGA group may be explained by the partly serotonergic effect that distinguishes flupentixol from other conventional antipsychotics (see later). Our data concerning neurocognitive outcomes generally suggest a lack of difference between both experimental groups and are thus in line with findings from the CATIE trial (Harvey, 2007; Keefe et al., 2007) that demonstrated similar neurocognitive effects of SGAs and the FGA perphenazine in a sample of 817 schizophrenia patients. However, in that study cognitive performance was just a tertiary outcome after discontinuation of treatment and psychopathology. The CATIE trail assessed a large sample of schizophrenia patients treated with the FGA perphenazine and different SGAs (risperidon, olanzapine, ziprasidone, quetiapine). However, the trial was characterized by certain methodological limitations (e.g. high drop-out rates, selection bias in the perphenazine group, partially

unblinded investigators). Therefore, the presence or, respectively, absence of group differences in this study, including the earlier mentioned lack of cognition effects, have to be interpreted cautiously (Hasan et al., 2013).

Based on Ehlis et al. (2012) which demonstrated a differential effect of FGAs and SGAs depending on initial 'hypofrontality', we included pre-treatment ACC function in the analysis of the ERN and found a differential increase in ERP values after errors specifically in patients with weak initial PFC function, independent of the medication. Previously, Ehlis et al. (2012) concluded that in patients with weak PFC function, SGAs were more effective due to their additional affinity for 5-HT receptors in the frontal lobe. In the present study, we compared quetiapine to flupentixol, an FGA that has also been seen as a partial atypical antipsychotic (Kühn et al., 2000) due to its antagonistic effect on 5-$HT_{2A}$ receptors. Thus, our results are in line with the findings of Ehlis and colleagues, considering an additional effect of flupentixol in prefrontal areas beyond the 'typical' effect on subcortical dopamine receptors. Whereas in the total group of flupentixol-treated patients a neurophysiological treatment effect was only adumbrated in prolonged ERN latencies, for patients with weak initial ACC function we could also observe the quetiapine-like effect on CRN/ERN amplitudes. At this point, however, it has to be stated that the representativeness of flupentixol for many other FGAs that do not share this specific binding profile will be rather restricted. Therefore, the present results cannot conclusively clarify the differential efficacy of quetiapine in comparison with other types of FGAs. Nonetheless, the present study is the first to present certain differences, but also similarities, in the treatment of neurocognitive dysfunction in schizophrenia with quetiapine and flupentixol. Moreover, as the similarities between flupentixol and quetiapine increase the risk for (often feared) missing group differences, the reported differential treatment effects appear to be linked to the specific differences between their profiles of action and the neurophysiological results show that ACC function seems to be sensitive to these differences.

Finally, correlation analyses revealed a significant relationship between ERN amplitudes and psychopathology scores at follow-up, indicating decreased psychotic symptomatology and improved social functioning with higher ERN. This finding indicates a functional relationship between the ERN and psychological variables that go beyond basal error-monitoring and confirm the importance of action-monitoring processes for general psychological functioning.

### *Limitations*

Although we strove to control for possibly confounding variables that may affect ACC function besides target medication, certain factors could not be held constant. In particular, as a matter of individualized treatment, some patients received different co-medication which could not be completely avoided, because the majority of patients were enrolled in the study during the phase of acute psychosis. Due to strongly enhanced anxiety and/or suicide risk, particularly benzodiazepines or anti-depressive drugs were administered to achieve clinical stabilization. Regarding anti-depressants, previous studies mainly indicate that chronic intake particularly affects the limbic system (Norbury et al., 2009; Ruhé et al., 2012). Although altered activity in the dorsal and ventral ACC was also reported, these effects were observed only in patients with unipolar and/or bipolar depressive disorder and therefore cannot be transformed unreservedly into schizophrenia patient samples. Furthermore, a recent study by Hester et al. (2012) demonstrated that methylphenidate, but not citalopram or atomoxetine, directly enhanced error awareness together with strengthened ACC activation differences for aware compared to unaware errors. Therefore, anti-depressive agents may not be crucial for error monitoring processes provided by the ACC. Apart from direct effects on frontal brain function, there may be interaction effects because SSRIs may cause a relevant inhibition of CYP enzymes which mediate antipsychotic medication metabolism (Spina and De Leon, 2007). Thus, SSRI co-medication may indirectly affect plasma concentrations of the antipsychotic agent. However, group comparisons concerning frequencies of SSRI co-medication revealed no significant differences, neither at baseline, nor at follow-up. With regard to lithium, group comparisons revealed similar results. Apart from anti-depressant agents, a non-negligible number of patients ($n$=17) received benzodiazepine (loracepam) medication on demand. This is particularly critical as benzodiazepines have been shown to influence cognition on the behavioural and neurofunctional (ACC) level (Mintzer et al., 2006; Munoz-Torres et al., 2011). Among other cognitive domains, error monitoring processes have been shown to be affected (Bruijn et al., 2004). With respect to working memory, ACC activity decreases induced by loracepam were also reported in a sample of schizophrenia patients (Menzies et al., 2007). Therefore, current co-medication with lorazepam needs to be regarded as a limitation of the present study because overall decreasing effects on action

monitoring/ACC function in the investigated sample cannot be ruled out. However, we argue that benzodiazepine intake did not affect between-group comparisons, as the number of patients receiving lorazepam did not differ between groups. To the best of our knowledge, there is no current evidence for differential interactions between benzodiazepine agents and SGAs *vs.* FGAs regarding the effects on ACC function. Accordingly, we do not expect augmented benzodiazepine intake to bias the reported group differences.

Beyond pharmacological issues, all study patients consistently received psychotherapy which may have contributed to behavioural outcome, i.e. symptom reduction, for which neurophysiologic effects are not directly assessable. The present results should therefore be interpreted cautiously under the consideration of additional factors that usually arise in schizophrenia treatment. The naturally high drop-out rate that is problematic in any treatment study, especially with psychotic patients, led to a somewhat small sample size of 31 patients. However, because statistical test power is naturally decreased for small samples, the discovered effects are all the more encouraging. Nevertheless, it would be preferable to replicate the present results in bigger study groups, especially with equal group sizes that were not achievable in the present study due to higher drop-out rates in the FG. The present findings should be further underpinned by means of spatially high-resolution imaging (e.g. fMRI) allowing for direct allocation of neurofunctional treatment effects to the ACC as well as usage of additional paradigms that target ACC function beyond action-monitoring paradigms.

## Conclusion

The present work represents a unique comparison of treatment effects induced by two specific antipsychotics in a prospective, randomized, rater-blind study. Electrophysiological data suggests that both agents trigger different mechanisms within the ACC: whereas ERP amplitudes indicated intensified action-monitoring for quetiapine treatment, ERP latencies suggested a prolongation of respective processes under flupentixol. If, however, only subjects with weak baseline ACC function were regarded, both agents were associated with a similar enhancement of CRN/ERN amplitudes over time, possibly triggered by an antagonistic effect of both agents on 5-$HT_{2A}$ receptors. As these distinct effects of atypical *vs.* typical antipsychotic treatment have, so far, not been reported, subsequent research is necessary to further elucidate the particular mechanisms underlying these effects.

## Acknowledgements

This study was an investigator-initiated trial, which was financially supported by AstraZeneca GmbH (Wedel, Germany). We thank Melanie Harder, Inge Groebner and Ramona Taeglich for their professional, trustworthy and strenuous support as the responsible study nurses, as well as Michael Bange for his diligent help during the data acquisition phase. Trial registry name: German Clinical Trials Register; registration identification number: DRKS00003934; registry URL: https://://drks-neu.uniklinik-freiburg.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00003934.

## Statement of Interest

In the past 3 yr, A.R. has received research grants from Astra Zeneca and PsyNova, which however had no influence whatsoever on the present study. In addition, A.R. was supported by the German Research Foundation (DFG; Grant RE1632/1-1, /1-3 and /5, KFO 125; SFB-TRR 58; RTG 1252). Over the past 3 yr, B.P. has received compensation for lectures from Pfizer Pharma and Janssen-Cilag, which had no influence on the present study. A.J.F. and A.-C.E. have been financially supported by the DFG (SFB-TRR 58, subproject C4). A.J.F. is further supported by the Federal Ministry of Education and Research (BMBF 01GV0610). The listed financial support is not related to the present work.

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